Dental and Skeletal Stem Cells: Potential Cellular Therapeutics for Craniofacial Regeneration

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Abstract: The study of stem cells has received considerable attention since the discovery that adult stem cells have the capacity to form many different tissue types. Technical advances have helped identify potential stem cells, and their capacity for regenerating tissues is being studied in transplantation models. Further study of the isolation, nature, and differentiation potential of stem cells will likely have a positive impact on our understanding of human development and regenerative medicine. This review highlights the difference between embryonic and adult stem cells and discusses the potential use of these cells for cellular therapeutics for craniofacial regeneration.

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The human body has a remarkable capacity for regeneration. Cells in tissues such as blood and epithelia divide rapidly and are regenerated continually throughout life, whereas cells in most other tissues turn over more slowly and respond only to specific biological signals.

The unique cells that give rise to specialized tissues are termed stem cells. Stem cells are extraordinary cells that have the capacity for self-renewal and can give rise to one and sometimes many different cell types. In mature tissue, these adult stem cells (ASCs) play a major role in homeostasis and tissue repair. Although such stem cells have been studied for decades, recent findings suggest that ASCs have astonishing and unanticipated capacities to develop into diverse tissues. Even more remarkable is the developmental capacity of embryonic stem cells. Embryonic stem cells (ESCs) can, in theory, give rise to all tissue types and, as such, provide much hope for understanding human development and for regenerative medicine.

Embryonic Stem Cells

In the simplest sense, a fertilized egg represents the fundamental stem cell because it is totipotent and can develop into a complete organism. In early development, the totipotent fertilized egg undergoes several rounds of rapid cell divisions before the cells begin to specialize. By the blastocyst stage of development, a specialized compartment called the inner cell mass begins to take shape. Cells within the inner cell mass have been termed embryonic stem cells (ECSs) (Figure 1). Murine ESCs can be genetically modified and are used to develop transgenic mice that have a deficient gene, overexpress it, or express a mutated form. These animal studies demonstrate that when placed into a developing embryo, ESCs have the capacity to form every type of cell found in the body. Scientists have learned to culture these ESCs and have demonstrated that they have an extraordinary ability to form many cell types. ESCs therefore may represent a repository of cells for po-

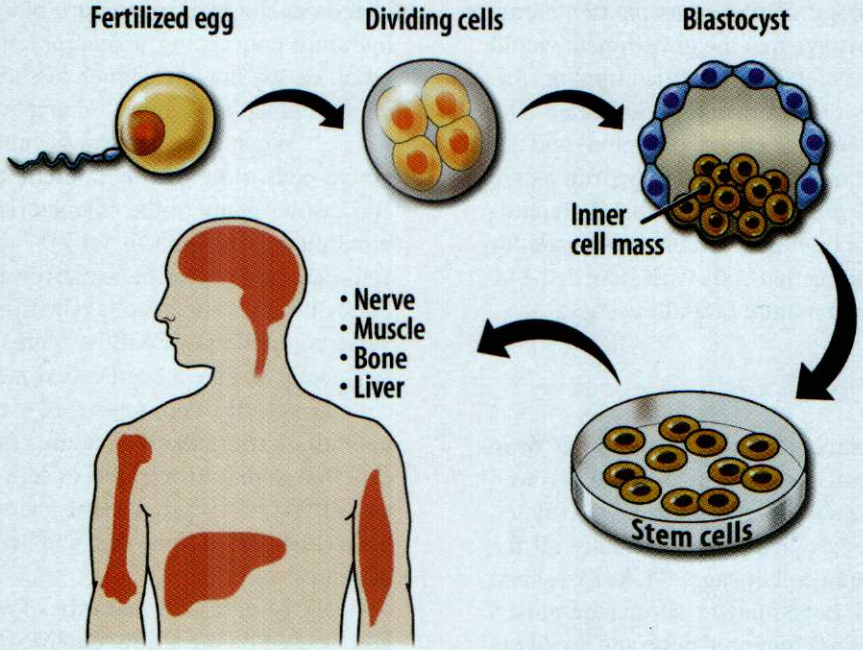

Figure 1. Stem cells derived from the inner cell mass of blastocyst stage human embryos have been shown to differentiate into several different cell types and have the potential to one day replace or regenerate tissues.

tential uses in regenerative medicine.[1,2] As embryonic development progresses and cells segregate into defined germ layers, their capacity to differentiate into different cell types is thought to become more restricted as specific organ systems are formed. However, so-called fetal stem cells that can be isolated from these developing organs also have been postulated to have a significant capacity to regenerate and repair damaged tissues.

There is great hope that pluripotent ESCs can develop into almost any tissue, ranging from neurons to muscle to perhaps teeth. Both laboratory-based and animal transplant studies have demonstrated that ESCs can be cultured and coaxed into forming nearly any cell. The mechanisms by which ESCs are able to differentiate into this broad array of cell types are not known, but it is clear that the local environment plays an important role. This potentially unlimited source of cells could one day relieve the heavy burden now placed on tissue replacement by whole organ transplantation.

The prospect of developing tissues by transplanted stem cells rather than whole organs has been reinforced by the development of culture techniques for human stem cells.[3,4] (See Figure 1.) Cells that were harvested from the inner cell mass of embryos from *in vitro* fertilization clinics or terminated pregnancies have been established and may serve as a source of unspecialized cells that maintain stem cell characteristics. This finding has led to the hope that severely debilitating human conditions like Alzheimer's and Parkinson's diseases will one day be treated with stem cell therapy.

However, at least two large obstacles stand in the way of this goal. The first is a technical hurdle—one that is far from trivial. Difficulty in manipulating the cells to reproducibly and predictably differentiate into the desired tissue, and no other, clearly indicates the many basic questions regarding the biology of stem cells that must be answered. Another equally challenging question that must be resolved is one of law and ethics. In the United States and several other countries, federal funds have not been available to conduct research on human ESCs. However, after considerable debate, the National Institutes of Health and the University of Wisconsin signed a memorandum of understanding that opened the door for restricted stem cell investigation. The agreement allows federal funding for research on existing stem cell lines that meet the criteria outlined by President Bush's August 9, 2001, address. Subsequently, a Stem Cell Registry has been established that lists seventy-eight cell lines from several international laboratories that meet the eligibility criteria.

While the decision to allow federal funding to investigate the biology of ESCs has pleased some, others expressed outrage that the government would allow research on any fetal cell obtained from *in vitro* fertilization clinics or terminated pregnancies. The seemingly insurmountable ethical dilemmas and debates will surely continue until the hope trumps the hype, or alternative methods are developed. Regardless of the technical or ethical issues, one reason for optimism is the finding that cells with stem cell-like activity also reside in mature or adult tissues.

Adult Stem Cells

The regenerative potential of ASCs has been recognized for several decades. For example, it is well established that hematopoietic stem cells isolated from adult tissues can give rise to virtually all the cell-types in the blood cell lineage.[5,6] Likewise, stem cells residing in the bone marrow stroma are poised to repair the occasional fractured bone and are likely responsible for repairing microfractures that occur on a daily basis.[7]

Adult stem cells were originally thought to have a rather restricted potential for generating new tissues; that is, hematopoietic stem cells could only make new blood cells. But recent studies have changed this perception. New observations suggest that, in addition to generating the derivatives of the blood system, stem cells within the bone marrow of an adult organism can also give rise to muscle[8] and neuron-like cells in the brain.[9] Perhaps even more astonishing, mouse central nervous system stem cells can differentiate into cells of other tissues such as muscle, blood, and heart, in addition to several types of nervous system cells.[10-12] If ASCs turn out to have the same potential as ESCs, some of the ethical issues surrounding ESCs may be overcome.

Mesenchymal Stem Cells

An ASC with which we have experience resides within the bone marrow of humans and many other species. Bone marrow is a complex tissue composed of the hematopoietic system and the bone marrow stroma, two distinct but interdependent biologic cell populations. Several studies have demonstrated the nature of cooperative interactions between these two cell populations. Hematopoietic cells influence the activity of the stromal cells, and in addition to serving as a mechanical support for differentiating hematopoietic cells, the bone marrow stroma also expresses cell-signaling factors that participate in the development of mature blood cells.[13] A vast literature concerning hematopoietic cell transplantation exists; however, much less attention has been paid to transplantation of bone marrow stroma.

When bone marrow is cultured *in vitro*, adherent cells of non-hematopoietic origin proliferate and exhibit many of the characteristics attributed to bone marrow stroma *in vivo*.[14-16] Cultured stromal cells derived from the bone marrow have been termed bone marrow stromal cells (BMSCs). Within the diverse population of BMSCs, there exists a subset of stem cells that have been called mesenchymal stem cells or skeletal stem cells that maintain the multipotential, differentiative features that define a stem cell; that is, they are capable of self-renewal and they can differentiate into several phenotypes including bone, cartilage, adipocytes, and hematopoiesis-supporting stroma.[17-18]

To date, the majority of work in this area has focused on the ability of BMSCs to differentiate into bone. Thus, *in vitro* expanded BMSCs may be a rich source of osteogenic progenitor cells that are capable of promoting the repair or regeneration of skeletal defects. Although BMSCs are inherently heterogeneous, the "plasticity" of this population provides unique scientific opportunities for investigating the role of BMSCs in skeletal homeostasis, genetically modifying potential stem cells, and the potential clinical utility of using autogenous cell therapies to increase the rate and extent of bone formation.

Bone Formation in Vivo

Cooperative cell-cell and cell-matrix interactions that occur during bone development have been studied in open transplant systems where BMSCs have been placed into defined anatomical sites such as under the kidney capsule of syngeneic animals. The disadvantages of investigating the osteogenic potential of BMSCs in kidney capsule transplants are that, in addition to being a technically difficult surgical procedure, only very small tissue samples are generated and the number of samples analyzed per recipient animal is limited. To overcome these limitations, recent studies have exploited the ability of immunocompromised mice to accept cell transplants from different strains and species of animals in a variety of anatomical sites that allow for multiple transplantations.[19] (See Figure 2.)

For open system transplants (that is, no barriers between donor and host cells or tissues), such as under the kidney capsule or subcutaneous sites, the use and nature of the transplantation vehicle clearly is an essential component required for successful osteogenesis. Osteogenesis does not proceed when bone marrow suspensions are injected subcutaneously or intramuscularly, when BMSCs are implanted as a cell pellet without a vehicle, or when BMSCs are implanted in rapidly resorbed vehicles.[20-22] Thus, it is evident that, in order to form bone, transplanted BMSCs require the presence of an organized framework to which they can adhere and proliferate for periods long enough to ensure differentiation and osteogenesis.

Potential Clinical Applications in the Orofacial Complex

Transplanted skeletal or dental stem cells may one day be used to repair craniofacial bone or even repair or regenerate teeth (Figure 3). While most often due to post-cancer ablative surgery, craniofacial osseous deficiencies can also arise from infection, trauma, congenital malformations, and progressive deforming skeletal diseases.[23-25] Techniques used to repair craniofacial skeletal defects parallel the accepted surgical therapies for bone loss elsewhere in the skeleton and include the use of autogenous bone and alloplastic materials. However, despite the usefulness of these reparative strategies, each method has inherent limitations that restrict their universal application.[26-28] Transplantation of a bone marrow stromal cell population that contains skeletal stem cells may provide a promising alternative approach for reconstruction of craniofacial defects by circumventing many of the limitations of auto- and allografting methods.[17]

To date, most studies have shown the effectiveness of stem cell regenerative therapy in experimental animal models. In this strategy, stem cells are expanded in the laboratory, loaded onto an appropriate carrier, and locally transplanted to the site of a bony defect. Successful regeneration of bony defects that would not otherwise heal by cells in the local microenvironment has been shown in both calvarial and long bones models.[29-32] Because of these successful findings in animal models, several centers are embarking on clinical trials to regenerate bone in humans.

Identification of Stem Cells in Other Mineralized Tissues in the Oral Cavity

In light of recent discoveries of adult stem cells in tissues that were not thought to contain stem cells, it was hypothesized that other hard tissues in the oral cavity may also contain these unique entities. Using techniques previously established to isolate progenitors from bone and marrow, it is now apparent that these tissues do in fact contain clonogenic cells with extensive proliferative capacity.[33] Furthermore, *in vivo* transplantation has further characterized their ability to regenerate hard tissue (Figure 2).

Isolation and Characterization of Cementoblast-Like Cells

Although there are differences in the organization of bone and cementum, it is not clear if they are formed by distinct cell types or by a bone-forming cell that has different environmental cues. Distinguishing between these two possibilities has been difficult because, to date, there is no specific marker for cementum or cementocytes. Cultures of murine[34] or primary human[35] cementum-derived cells (HCDCs) have been established from healthy teeth using a collagenase pretreatment as had been established previously for the culture of trabecular bone cells. With primary human cementum-derived cells, discrete colonies that contained cells exhibiting fibroblast-like morphology formed, and when the colonies became sufficiently large, cells from individual colonies were isolated and subcultured.

Cementum-derived cells exhibit low levels or no alkaline phosphatase activity and mineralize *in vitro* to a lesser degree than BMSC cultures. To study the differentiation capacities of HCDCs, cells were attached to hydroxyapatite/tricalcium phosphate ceramic and transplanted subcutaneously into immunocompromised mice. Like individual colonies of human BMSCs, approximately 50 percent of the clonal HCDCs tested formed a bone-like tissue that featured osteocyte/cementocyte-like cells embedded within a mineralized matrix. However, the mineralized tissue was lined with a layer of cells that were somewhat more elongated than osteoblasts, and the

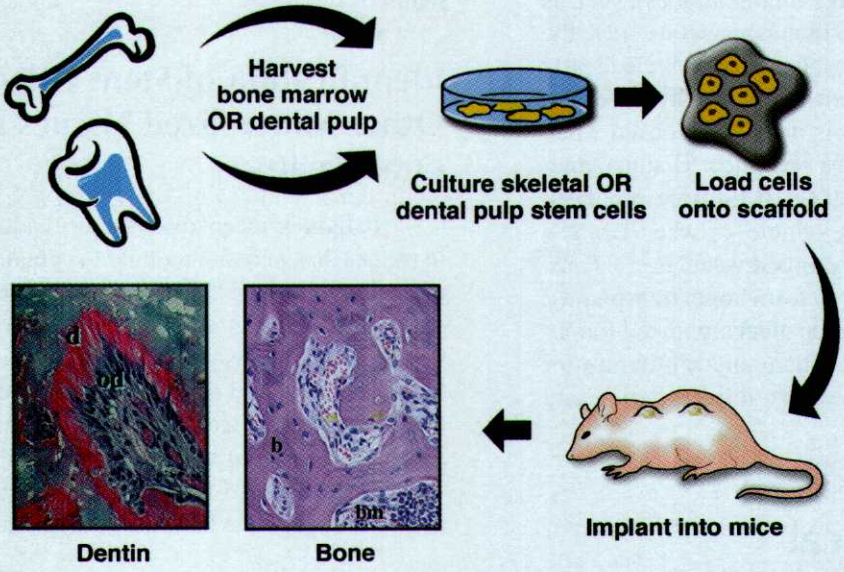

Figure 2. Transplantation studies have shown that human stem cells from the bone marrow or dental pulp can form bone or dentin *in vivo*.[19,33] In this strategy, stem cells are harvested from the bone marrow or dental pulp, expanded in the laboratory, loaded onto an appropriate carrier, and locally transplanted into subcutaneous pouches in mice. The *in vivo* environment allows the stem cells to differentiate and form tissues such as bone or dentin. d is dentin, od are odontoblasts, b is bone, and bm is bone marrow.

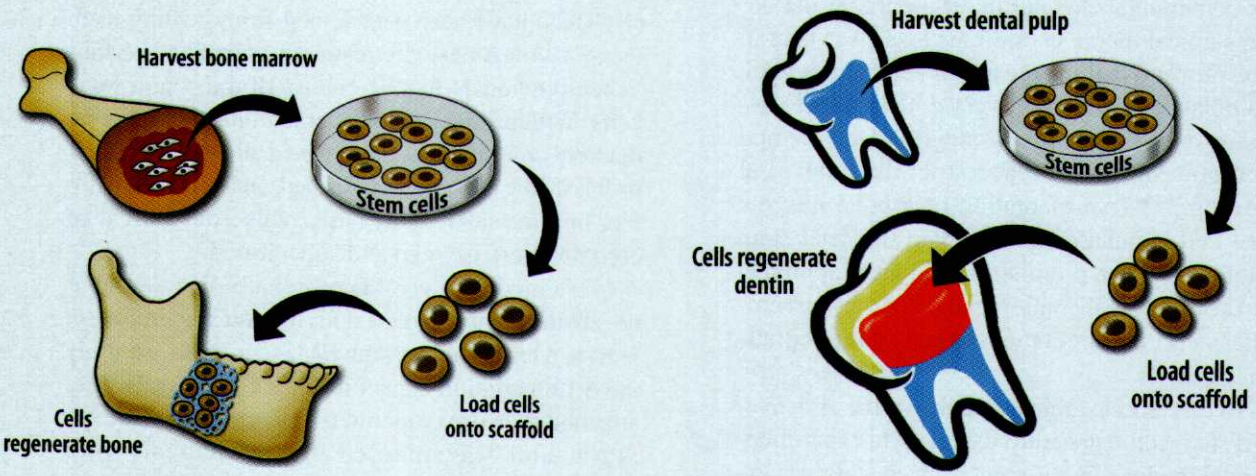

Figure 3. Adult stem cells can be harvested from the bone marrow or dental tissues such as the dental pulp and expanded in the laboratory. When loaded onto appropriate scaffolds and transplanted back into a deficient site, stem cells have the potential to regenerate bone and tooth structures.

HCDC matrix was somewhat less cellular than that produced by BMSCs. Unlike BMSC transplants, which developed lamellar bone, the HCDC matrix was found to contain unorganized collagen bundles, as is seen in cementum. Cells in the HCDC matrix were positive for fibromodulin and lumican, while osteocytes in the BMSC matrix were negative. The HCDC transplants were also devoid of hematopoietic marrow.

These results show that cells from normal human cementum can be isolated and expanded *in vitro*. Furthermore, these cells are capable of differentiating and forming a cementum-like tissue when transplanted into immunocompromised mice.[35,36]

Adult Human Dental Pulp Stem Cells

Another mineralized tissue that has a great deal of similarity to bone is dentin. Although dentin is not turned over throughout life, as is bone, limited dentinal repair in the postnatal organism does occur. It was postulated that the ability for limited repair is maintained by a precursor population, associated with pulp tissue, that has the ability to mature into odontoblasts. Clonogenic and highly proliferative cells have been derived from enzymatically disaggregated adult human dental pulp, which have been termed dental pulp stem cells (DPSCs), that form sporadic, but densely calcified nodules *in vitro*. When DPSCs were transplanted with hydroxyapatite/tricalcium phosphate into immunocompromised mice, they generated a dentin-like structure with collagen fibers running perpendicular to the mineralizing surface as is found *in vivo*, and contained the dentin-enriched protein, dentin sialo-phosphoprotein. The newly formed dentin was lined with human odontoblast-like cells that extended long cellular processes into the mineralized matrix, and surrounded an interstitial tissue reminiscent of pulp *in vivo* with respect to the organization of the vasculature and connective tissue (Figure 2). In contrast to BMSCs, DPSCs did not support the establishment of a hematopoietic marrow or adipocytes, elements that are also absent in dental pulp tissue *in vivo*.[33]

By immunophenotyping, the DSPCs are virtually identical to BMSCs, yet each population produces quite different mineralized matrices. To identify possible differences between these two populations, their gene expression profiles were characterized using a commercially available microarray. Human DPSCs and BMSCs were found to have a similar level of gene expression for more than 4,000 known genes represented on the filter. A few differentially expressed genes including collagen type XVIII alpha 1, insulin-like growth factor 2, discordin domain tyrosine kinase 2, NAD(P)H menadione oxidoreductase, homolog 2 of Drosophila large disk, and cyclin-dependent kinase 6 were highly expressed in DPSCs, while insulin-like growth factor binding protein 7 and collagen type I alpha 2 were more highly expressed in BMSCs. This study provides a basis to further characterize the functional roles of the differentially expressed genes in the development of dentin and bone.[37]

Prospectus

Clearly, advances in adult stem cell biology have provided a great deal of impetus for the biomedical community to translate these findings into clinical application. Given the fact that we have in hand populations of stem cells that reproducibly reform bone and its marrow, cementum, dentin, and perhaps even periodontal ligament, it is possible to envision complete restoration of the hard tissues in the oral cavity using the patient's own cells, thereby avoiding issues of histocompatability. Furthermore, advances in techniques to genetically modify the gene activity of stem cells during their *ex vivo* expansion offers the unique possibility to make a patient's own stem cells even better. For example, the activity of genes that regulate the aging process can be modified, thereby "rejuvenating" the stem cells and giving them a new lease on life. Another example relates to the molecular engineering of stem cells derived from patients with genetic diseases.

In these cases, there is the possibility of replacing a gene activity that is missing or silencing a gene activity that is defective. However, replacing dental tissues with either cell- or gene-based therapy may be complicated in areas of unresolved inflammation,[38] thus highlighting the need for more research to understand potential complicating factors. While the technical hurdles to achieve these goals should not be underestimated, the recent recognition of stem cells and their role in tissue regeneration provide a strong basis upon which we can begin to actually impact on the clinical management of craniofacial defects.

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Nominations Invited for 2003-04 President-Elect

All ADEA members are invited to nominate candidates for the Association's 2003-04 President-Elect. The Nominating Committee consists of the Immediate Past President, Pamela Zarkowski, and the seven Council Vice Presidents.

The nomination process is as follows:

- A call for nominations is placed in the *Bulletin of Dental Education* and in the *Journal of Dental Education* from March through October.
- All members are invited to nominate as many individuals as they wish, including themselves.
- The Council Administrative Boards are also invited to nominate candidates; however, these boards will not be informed of the identity of the other candidates. In order to maintain confidentiality, only the Nominating Committee will know the identity of all the nominees.
- In addition to receiving nominations, the Nominating Committee may actively seek qualified candidates.
- Each nominee should submit a one-page biographical statement by the deadline of November 1, 2002.
- Between November 1 and December 31, 2002, the Nominating Committee will meet to recommend one or more candidates to stand for election.
- Additional nominations may be made by delegates from the floor at the Opening Session of the House of Delegates at the 2003 Annual Session next March in San Antonio. The delegates vote with secret ballots during the course of the Annual Session, and the winner is announced at the Closing Session of the House of Delegates.

Nominations, with a one-page biographical statement, should be mailed in confidence to Dr. Richard W. Valachovic, Executive Director, Attn: Nominating Committee, ADEA, 1625 Massachusetts Ave., NW, Suite 600, Washington, DC 20036-2212